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Original article

Impact of chemotherapy followed by aromatase inhibitors on bone health of women with ER-positive early breast cancer in real world clinical settings in Greece: Results of the POCHARBI trial conducted by the Hellenic Society of Breast Surgeons

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ABSTRACT

Introduction: The aim of this observational study was to assess the combined impact of chemotherapy (CT) and aromatase inhibitors (AI) therapy on bone mineral density (BMD) in postmenopausal women with estrogen receptor (ER)-positive early breast cancer.
Methods: Patients were treated with a third generation AI, either as adjuvant therapy (HT cohort, n = 166) or as subsequent endocrine therapy after initial treatment with chemotherapy (CT cohort, n = 124), and were followed up for a 12-month period. BMD was evaluated at lumbar spine (LS) and total hip (HP) before CT, before AI therapy and after 12 months of AI therapy. The primary study objective was changes in LS BMD between pre CT treatment and post 12 months AI therapy in the CT cohort.
Results: There were no statistically significant changes in LS BMD, either within CT or HT cohort. In the CT cohort, the mean LS BMD change was −0.72% (95% CI: −2.97%, +1.53%, p = 0.5526) between CT start and month 12 of AI therapy, while it was −0.19% (95% CI: −2.12%, +1.74%, p = 0.8309) and −0.59% (95% CI: −3.18%, +2.00%, p = 0.4759) between CT start and AI start and AI start and month 12 of AI therapy respectively. The mean change in LS BMD in the HT cohort (i.e. after 12 months of AI treatment) was +1.51% (95% CI: −0.96%, +3.98%, p = 0.7420).
Conclusions: The results of this study indicate that, under routine clinical practice, most postmenopausal patients who receive CT before AI therapy do not experience debilitating BMD consequences during the first year of AI treatment.
Trial registration: ClinicalTrials.gov Identifier NCT01298362.

Introduction

Breast cancer still represents in the 21st century the most common malignancy in Europe (13.5% of all cancer cases) [1] and the second ranked cause of death from cancer among women in developed countries [2]. Although chemotherapy and hormonal therapies have been shown to have a profound, positive impact on survival in hormone-sensitive BC patients, hormonal therapy with Aromatase Inhibitors (AIs) has the potential to lead to significant bone loss primarily through the disruption of the bone-enhancing properties of estrogen [3]. AIs, widely used in the adjuvant and metastatic setting, decrease the production of adrenal estrogens [4] and are associated with an increased risk of fractures and bone loss of approximately 2% per year [5]. The bone marrow micro-environment is intimately involved in the metastatic processes required for cancer dissemination, and there are emerging data showing that, at least in some clinical situations, the use of bone-targeted treatments, such as potent bisphosphonates or denosumab, can reduce metastasis to bone and has potential impact on patient survival [6]. Following the ESMO guidelines, patients with pre-treatment osteopenic to osteoporotic status should be treated

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with a combination of both therapies in order to avoid bone loss induced by aromatase inhibition [6].

These findings were also highlighted in the ARBI trial [7], concluding that even in post-menopausal BC patients with very low risk to develop osteoporosis, addition of oral risedronate after anastrozole has a favorable effect on BMD.

Chemotherapy can have both direct and indirect impact on the bone microenvironment, ultimately leading to decreased BMD [5]. In particular, the age specific bone density z scores of post-menopausal women who received adjuvant chemotherapy were ~0.5 SD lower than women who had not received chemotherapy suggesting that chemotherapy can have direct, non-hormonal effects on the skeleton [8]. The majority of clinical trials on AIs therapies have assessed their effect on bone health either in comparison with tamoxifen or use after pretreatment with tamoxifen making interpretation of the findings difficult. However, the combined impact on BMD of different therapeutic approaches pertaining to the initial administration of chemotherapy followed by AIs has not yet been established. It is therefore crucial to identify the overall impact of this therapeutic approach on bone loss as well as the incidence of bone fractures in a real life clinical setting where BC patients previously treated with chemotherapy initiate AI without having previously been exposed to tamoxifen.

In view of this need, the Hellenic Society of Breast Surgeons designed this multicenter, observational study of women with ER-positive, early BC treated with an AI either as adjuvant therapy or as subsequent endocrine therapy after initial treatment with chemotherapy. The primary aim was to assess the combined impact of chemotherapy and AIs on BMD, as well as the incidence of therapy associated fractures in this highly sensitive group of women who combine the increased risk of osteoporosis due to their post-menopausal status and the anticancer therapy they receive.

Methods

Subject population

Female patients, at the age of 40 or older, with ER-positive early BC, who received therapy with a third generation AI either as adjuvant hormonal treatment or as subsequent endocrine therapy after first-line anthracycline- and/or taxane-based chemotherapy for a period no longer than 1 month (4 weeks) prior to inclusion, were eligible for entering the study. Patients, who received the AI as subsequent endocrine therapy, had been rendered postmenopausal prior to chemotherapy commencement and were at least 12 months from last menstrual period. For subjects who were amenorrheic for <12 months (including patients who underwent hysterectomy, or received ERT/HRT), they should have serum FSH $\geq$50 UI/L before the commencement of AI therapy. Furthermore, patients should have available data on LS and HP BMD prior to chemotherapy initiation as well as before the commencement of AI therapy, and provide written informed consent. Calcium and vitamin D supplementations were recommended treatments prior and throughout the study.

Exclusion criteria were, prior administration of other endocrine therapy (including tamoxifen), chemotherapy-induced menopause, involvement in the planning and conduct of the study, participation in another clinical study within a period of 3 months prior to any study related procedures, evidence of diseases known to interfere with bone metabolism, such as hyperparathyroidism, hyperthyroidism, osteomalacia, etc., and evidence of metastatic disease or abnormal clinical laboratory parameters that were assessed as clinically significant by the investigator. Other exclusion criteria were: patients with normal BMD or mild osteopenia (T-score ≥ -2 in either site) receiving oral or IV bisphosphonate treatment and patients with severe osteopenia or osteoporosis (T-score ≤ -2 in either site) receiving IV bisphosphonate treatment (oral bisphosphonate treatment was allowed). Finally, patients that received bisphosphonate treatment either orally or IV, prior to chemotherapy commencement, patients that stopped hormone-replacement therapy (HRT) less than 3 months prior to chemotherapy commencement, and patients that received neoadjuvant therapy were not included in the study.

Study design

Two-hundred ninety post-menopausal patients with ER-positive early BC were included in this observational 2-cohort study from 12 centres in Greece. The total planned study duration was 24 months comprising of a recruitment period of 12 months and a follow-up period of 12 months for each participating subject.

The study was completed in two visits, while the treatment administered to the participating subjects was determined by the physician according to the approved drug labels within the normal clinical practice. Patients were treated with a third generation AI, either as adjuvant therapy (HT cohort) or as subsequent endocrine therapy after initial treatment with chemotherapy (CT cohort), and were followed up for a 12-month period.

BMD was evaluated at LS and HP with measurements taken before CT, before AI therapy and at the end of the 12 month follow-up period while on AI treatment. Dual Energy X-Ray Absorptiometry (DEXA scan) was used with all measurements performed with the Explorer absorptiometer produced by Hologic, Bedford, MA, USA in the same referral site in Athens, apart from two centres in other cities which used however the same absorptiometer model with identical software.

The primary outcome variable was the mean percentage change in LS BMD between the pre CT treatment measurement and the post 12 months AI measurements in the CT cohort. The HT cohort was included as a control group.

The secondary outcome variables were:

- Mean percentage change in HP BMD between the pre CT treatment measurement and the post 12 months AI measurements in the CT cohort.
- Mean percentage change in LS and HP BMD between the pre CT treatment measurement and the pre AI treatment measurement in the CT cohort.
- Mean percentage change in LS and HP BMD from AI commencement to month 12 of AI therapy in each cohort.
- Self-reported bone fracture rate.

This study was initiated only after all required legal documentation (Study protocol and Informed Consent Form) had been reviewed and approved by the respective Institutional Review Board/Independent Ethics Committee and Competent Authority according to the national regulations. The ClinicalTrials.gov identifier is NCT01298362.

Sample size

Sample size calculation was based on the following considerations. According to available published data [9,10,11] the estimated mean percentage change in LS BMD due to AIs only was expected to be approximately 2.6% whereas the combined effect of chemotherapy and AIs was expected to be 7.5%, with a 1.5% expected standard deviation.

Thus, 100 patients in each cohort (200 patients in total) were needed in order to estimate the aforementioned mean changes